United States Court of Appeals for the Federal Circuit

DAIICHI SANKYO COMPANY, LTD., AND DAIICHI SANKYO, INC.,
Plaintiffs/Counterclaim

Defendant-Appellees,

v.

MATRIX LABORATORIES, LTD., MYLAN INC., MYLAN LABORATORIES, INC., AND MYLAN PHARMACEUTICALS, INC.,
Defendants-Counterclaimant-Appellants.

2009-1511

Appeal from the United States District Court for the District of New Jersey in Case No. 06-CV-03462, Judge William J. Martini.

Decided: September 9, 2010

DOMINICK A. CONDE, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiffs/counterclaim defendant-appellees. With him on the brief were LISA B. PENSABENE and JOSHUA I. ROTHMAN. Of counsel on the brief were HENRY B. GUTMAN, ROBERT

A. BOURQUE and NOAH M. LEIBOWITZ, Simpson Thacher & Bartlett LLP, of New York, New York.

ROBERT L. BYER, Duane Morris LLP, of Pittsburgh, Pennsylvania, argued for defendants/counterclaimant-appellants. Of counsel on the brief were SHANNON M. BLOODWORTH, Perkins Coie LLP, of Washington, DC, and DAVID J. HARTH, The Law Office of David J. Harth, of Madison, Wisconsin. Of counsel was DAN L. BAGATELL, Perkins Coie Brown & Bain P.A., of Phoenix, Arizona.

Before LOURIE, FRIEDMAN, and LINN, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Matrix Laboratories, Ltd., Mylan Inc., Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc. (collectively, "Mylan") appeal from the final decision of the United States District Court for the District of New Jersey sustaining the validity of U.S. Patent 5,616,599 ("the '599 patent") under 35 U.S.C. § 103. We affirm.

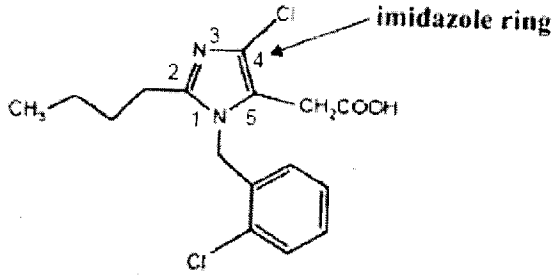
BACKGROUND

I.

Daiichi Sankyo Company, Ltd. and Daiichi Sankyo, Inc. (collectively, "Daiichi") own the '599 patent, which claims 1-biphenylmethylimidazole compounds and their use as angiotensin receptor blockers ("ARBs") for the treatment of high blood pressure. Claim 13 of the '599 patent covers the chemical compound olmesartan medoxomil, an ARB approved by the Food and Drug Administration ("FDA") and commercialized by Daiichi as the active ingredient in Benicar®, Benicar HCT®, and Azor®.

The invention of olmesartan medoxomil as an effective ARB built on years of research beginning in the

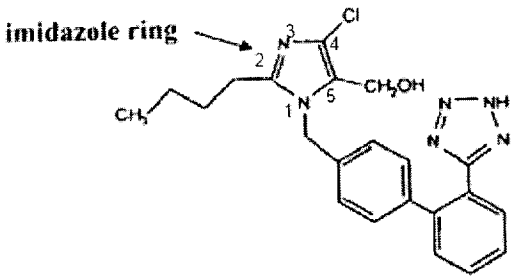
1970s, when scientists first came to appreciate the role of the angiotensin protein in controlling blood pressure. The first non-protein, small molecule ARBs were developed in the late 1970s and early 1980s by the Japanese pharmaceutical company Takeda Pharmaceutical Co. Ltd. ("Takeda"). These compounds each comprised an imidazole ring—a five-membered ring of the formula $C_3H_4N_2$—to which other chemical moieties were bonded at the 1-5-positions of the ring. One Takeda compound, S-8307, possessed a chlorophenyl group bonded through a methylene group at the 1-position, a butyl group (-C_4H_9) at the 2-position, a chlorine atom (-Cl) at the 4-position, and an acetic acid moiety (-CH_2COOH) at the 5-position. The chemical structure of S-8307 is pictured below with the ring's 1-position nitrogen positioned at the bottom of the ring.



S-8307
(Takeda)

The Takeda compounds, however, bound only weakly to the angiotensin receptor and thus were of little therapeutic value. Nevertheless, using Takeda's compounds as leads, scientists at E. I. du Pont de Nemours and Company ("DuPont") embarked on their own ARB research program with the aim of developing new compounds with

increased receptor-binding activity. DuPont's research led to the discovery of the first orally active ARB, known as losartan, which exhibited ten-fold greater binding affinity than the Takeda compounds. To obtain losartan, DuPont modified Takeda's S-8307 at the 1- and 5-positions of the imidazole ring: At the 1-position, DuPont added a second phenyl group with a tetrazole group attached, generating a biphenyltetrazole substituent. At the 5-position, DuPont replaced the acetic acid group with a hydroxymethyl group (-CH_2OH), which is metabolized to a carboxylic acid (-COOH) in the body. The chemical structure of losartan is depicted below.



LOSARTAN
(DuPont)

DuPont disclosed losartan in U.S. Patent 5,138,069 ("the '069 patent") along with more than four hundred structurally related ARBs. The '069 patent also discloses binding affinity data, measured as IC_{50} values,[1] for over two hundred compounds, including forty-two in losartan's biphenyltetrazole series. Chemists were able to use the

[1] The half maximal inhibitory concentration, or IC_{50}, represents the concentration of an inhibitor that is required for 50% inhibition of its target, and thus the effectiveness of an inhibitor. More specifically, a lower IC_{50} indicates a higher affinity binding.

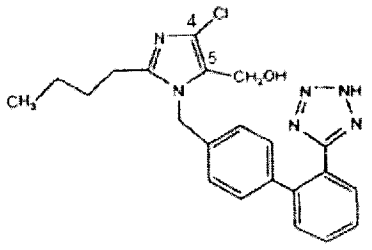
data disclosed in the '069 patent to uncover correlations between the compounds' structures and their binding affinities, called "structural-activity relationships" ("SARs"), which they could then use to guide the development of even more potent ARBs. For example, if the presence of a certain chemical moiety or type of chemical moiety at a given position correlates with an increase in binding affinity, chemists could attempt to use that chemical moiety or type of moiety in the next generation of ARBs, and they did.

Following losartan's success, over twenty different pharmaceutical companies, including Daiichi, established research programs to develop the next generation of ARBs. Daiichi's program resulted in the synthesis of olmesartan, the active metabolite of olmesartan medoxomil. Like losartan, olmesartan consists of an imidazole ring containing a biphenyltetrazole substituent at the 1-position and an alkyl group (propyl rather than butyl) at the 2-position. At the 4-position, however, olmesartan replaced losartan's lipophilic, or fat-loving, chlorine atom with its opposite, a hydrophilic, or water-loving, hydroxyisopropyl group ($-C(CH_3)_2OH$).[2] Of the compounds disclosed in DuPont's '069 patent, the vast majority contain a lipophilic group at the ring's 4-position. One compound with a hydrophilic group is losartan's regioisomer,[3] Example 118, in which the 4- and 5-positions on the imida-

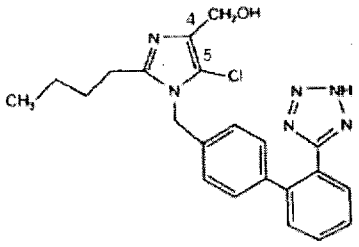
[2] When one speaks of replacing one group with another, it is understood that the "replacement" is not accomplished merely by writing it on paper and that an actual change from one group to another more often occurs by a new synthesis using different starting materials, *i.e.*, a chlorine atom is not directly replaced with a hydroxyisopropyl group.

[3] A regioisomer of another compound is one in which substituents around a ring are the same, but varied in position.

zole ring are reversed. The transposition results in a compound with a chlorine atom at the 5-position and a hydrophilic hydroxymethyl group (-CH_2OH) at the 4-position, as shown below.

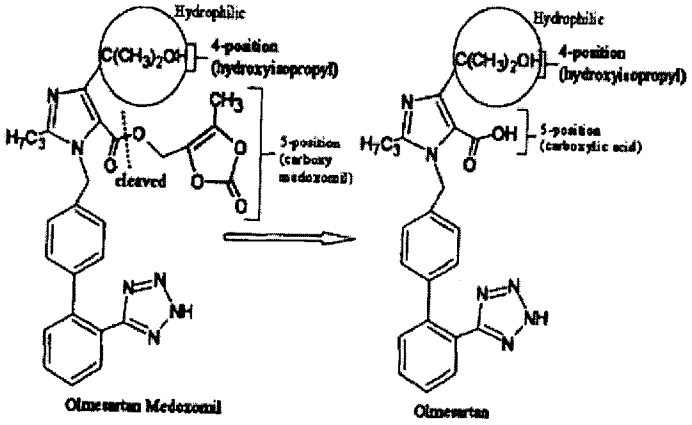


LOSARTAN

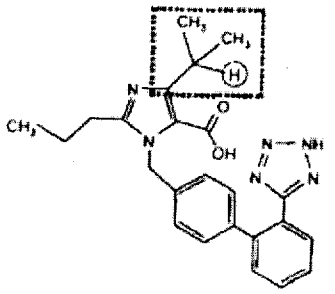


EXAMPLE 118

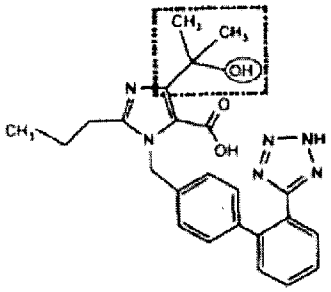
Olmesartan medoxomil also differs from losartan at the 5-position. Daiichi replaced losartan's hydroxymethyl group with a carboxy group masked by a medoxomil prodrug substituent to improve oral absorption. Like the hydroxymethyl group, the medoxomil moiety is metabolized to the carboxylic acid in the body. The structures of olmesartan medoxomil and olmesartan are depicted below.



Other second-generation ARBs, all prior art to olmesartan medoxomil, include DuPont's DuP 532, in which losartan's chlorine at the 4-position is replaced with multiple lipophilic fluorine atoms (-C_2F_5), and six compounds disclosed in DuPont's U.S. Patent 5,137,902 ("the '902 patent"), each of which has a more lipophilic alkyl group at the 4-position. The ARBs disclosed in DuPont's '902 patent ("the '902 compounds" or "the '902 ARBs") are the closest structurally to olmesartan, with Example 6 differing from olmesartan by only a single oxygen atom at the 4-position, as depicted below



'902 Example 6



Olmesartan

Other second-generation ARBs differ more significantly from losartan by not containing an imidazole ring, including Merck & Co., Inc.'s L-158,809 compound, Ciba-Geigy Corp.'s valsartan, and Eisai Inc.'s E-4177 compound.

II.

Mylan filed multiple Abbreviated New Drug Applications ("ANDAs") with Paragraph IV certifications under the Hatch-Waxman Act, 21 U.S.C. § 355, challenging the '599 patent and seeking FDA approval to manufacture generic olmesartan medoxomil in various dosages and combinations. Daiichi responded by filing suit against Mylan for patent infringement in the United States District Court for the District of New Jersey. The parties stipulated to infringement of claim 13, leaving only Mylan's counterclaim that claim 13 would have been obvious in light of (1) the second-generation ARBs in DuPont's '902 patent, which Mylan alleged one of skill in the art would have been motivated to select as lead compounds; (2) Example 118, losartan's regioisomer, in DuPont's '069 patent, which Mylan alleged would have motivated one of skill in the art to modify the '902 compounds' lipophilic alkyl groups at the 4-position with olmesartan's hydro-

philic hydroxyalkyl group; and (3) the well-known use of medoxomil as a prodrug.

After a ten-day bench trial, the district court held, in a comprehensive and well-reasoned opinion, that claim 13 of the '599 patent was not invalid as obvious. *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359 (D.N.J. 2009). The court determined that Mylan had failed to show by clear and convincing evidence that one skilled in the art would have chosen the '902 ARBs as lead compounds over other better-studied ARBs with greater potency and thus had failed to establish a *prima facie* case of obviousness. *Id.* at 376-77. The district court went on to find that, even assuming that Mylan had shown the '902 ARBs to be leads, the structure of the '902 compounds differed significantly from olmesartan medoxomil, *id.* at 377-78, and that, even assuming structural similarity, Mylan had failed to prove that one of skill in the art would have been motivated to modify the 4- and 5-positions of the '902 ARBs to obtain olmesartan medoxomil, *id.* at 378-81. Regarding the 4-position, the court found that the emphasis on lipophilicity in both the '069 patent and the second-generation ARBs taught away from the use of a hydrophilic group at the 4-position and from any expectation that the use of a hydrophilic group would generate an ARB with significantly improved biological properties. *Id.* at 370-75, 378-80. Regarding the 5-position, the court found that converting olmesartan into a prodrug was a disfavored and unpredictable approach and that medoxomil was a disfavored prodrug. *Id.* at 380.

Finally, the district court concluded that even if Mylan had established a *prima facie* case of obviousness, secondary considerations counseled against a finding of obviousness. *Id.* at 381. Specifically, the court found evidence of unexpected results in olmesartan medoxomil's enhanced potency and other favorable biological proper-

ties. *Id.* at 382-84. The court also found evidence of commercial success based on the significant market penetration of Benicar® despite being the seventh ARB on the market and despite Daiichi spending roughly the same amount in marketing as its competitors. *Id.* at 384-86.

On August 6, 2009, the district court entered final judgment and permanently enjoined Mylan's commercialization of olmesartan medoxomil until the expiration of the '599 patent. Mylan appealed. We have jurisdiction pursuant to 19 U.S.C. § 1295(a)(1).

DISCUSSION

Under the Patent Act, "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). While the ultimate determination of obviousness under § 103 is a question of law, it is based on several underlying factual findings, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). After a bench trial, we review the district court's conclusions of law *de novo* and findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is clearly erroneous if, despite some supporting evidence, a reviewing court is left with the definite and firm conviction that a mistake has been

made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

When a patent claims a chemical compound, a *prima facie* case of obviousness under the third *Graham* factor frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*) ("This court . . . reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness."); *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old. *Eisai*, 533 F.3d at 1357; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). In keeping with the flexible nature of the inquiry after *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the motivation to select and modify a lead compound need not be explicit in the art. *Eisai*, 533 F.3d at 1357; *Takeda*, 492 F.3d at 1356-57.

Mylan challenges, as it must to prevail, every step in the district court's decision holding that Mylan failed to establish its *prima facie* case that olmesartan medoxomil would have been obvious in light of the prior art. Specifically, Mylan challenges the district court's finding that one of skill in the art would not have selected the six ARBs in DuPont's '902 patent as lead compounds, pointing to evidence that the '902 compounds are undisputedly

the closest prior art. Mylan also challenges the court's finding that the '902 ARBs are not structurally similar to olmesartan medoxomil, arguing that one of the '902 compounds differs from olmesartan by only a single oxygen atom. Mylan also argues that the district court erred in finding no motivation to modify the '902 compounds at the 4- and 5-positions to arrive at olmesartan medoxomil when the '069 patent specifically taught a compound with a hydroxyalkyl group at the 4-position and the art taught medoxomil as a well-known prodrug for improving oral activity. Finally, Mylan contends that, contrary to the district court's finding, one of skill in the art would have had a reasonable expectation that modifying the '902 compounds to obtain olmesartan medoxomil would result in a similarly effective ARB.

In response, Daiichi defends the factual findings underlying the district court's determination that claim 13 of the '599 patent was not invalid as obvious. Daiichi first argues that the district court correctly found that one of skill in the art would not have been motivated to select the '902 ARBs as lead compounds over other more potent and better-studied prior art ARBs. Daiichi next asserts that the district court correctly found no motivation to modify the '902 compounds to create olmesartan medoxomil based on the lack of structural similarity between the '902 ARBs and olmesartan medoxomil, the existence of thousands of possible modifications, the illogic of selecting the '902 compounds as leads only to reject their distinguishing characteristic of increased lipophilicity at the 4-position, the fact that the prior art taught away from such an alteration at the 4-position, and the unpredictability associated with the use of a prodrug in general and medoxomil in particular. Finally, according to Daiichi, the district court correctly found no reasonable expecta-

tion that the proposed modifications would lead to an ARB with significantly improved activity over losartan.

We agree with Daiichi that the district court did not err in holding that Mylan failed to establish a *prima facie* case of obviousness. Specifically, we agree that Mylan failed to show that one of ordinary skill in the art would have been motivated to select the '902 ARBs as lead compounds or, even if they had, that the skilled artisan would have been motivated to modify the '902 compounds to synthesize olmesartan medoxomil, the claimed invention. We address each in turn.

I. Selection of a Lead Compound

In rejecting the '902 ARBs as lead compounds, the district court accepted as true all of Mylan's evidence on the '902 compounds, including that they represented a continuation of DuPont's work on the ARBs disclosed in the '069 patent, including losartan, and thus could take advantage of the '069 patent's SAR data, and that the preferred '902 compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives" with "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." *Daiichi Sankyo*, 670 F. Supp. 2d at 376 (alternations in original). Nevertheless, the court found that a medicinal chemist of ordinary skill would not have been motivated to select the '902 compounds over other second-generation ARBs, including L-158,809, DuP 532, the Eisai compounds, and valsartan, because many of the latter ARBs demonstrated greater potency and all had been more thoroughly studied than the '902 ARBs. Specifically, the court found that L-158,809 had 180 times, Example 7 of the Eisai compounds had 100 times, and DuP 532 had seven times the potency of losartan. *Id.* The court also found that while the '902 patent disclosed

in vivo oral activity, the prior art included not only data on oral activity for all but the Eisai compounds, but also data on the binding affinity and intravenous activity for L-158,809, the Eisai compounds, DuP 532, and valsartan as well as selectivity data for L-158,809 and DuP 532. *Id.* Finally, the court found that DuP 532, which shared losartan's imidazole-biphenyltetrazole backbone, could also benefit from the '069 patent's SAR data. *Id.* We see no clear error in the court's findings.

Mylan argues that because the '902 ARBs are undisputedly the closest prior art, that "should have been dispositive of the lead compound issue." Appellant Principal Br. 25. That argument runs contrary to our case law. In *Takeda*, we upheld a district court's finding that one of skill in the art would not have chosen the structurally closest prior art compound, compound b, as the lead compound in light of other compounds with more favorable characteristics. 492 F.3d at 1357-59. We reached the same result in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1377-79 (Fed. Cir. 2006). These cases illustrate that it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Accordingly, proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. *See Eli Lilly*, 471 F.3d at 1377-

79. Potent and promising activity in the prior art trumps mere structural relationships.

Mylan further faults the district court for not following this court's "clarification that a 'lead compound' analysis does not require identification of a single, best, compound as a starting point" but "the prior art may point to more than a 'single lead compound for further development efforts.'" Appellant Principal Br. 24 (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). But that misinterprets the district court's decision. As described above, the district court selected multiple compounds as leads, just not the compounds disclosed in the '902 patent. *Daiichi*, 670 F. Supp. 2d at 376. Contradicting itself, Mylan also faults the district court for selecting only five potential leads and for not including the '902 compounds among that finite number. While the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound, *see Altana Pharma*, 566 F.3d at 1008, the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art. Here, the district court did not commit error, let alone clear error, in finding that Mylan failed to meet that burden.

II. Motivation to Modify

The district court next found that, even accepting the '902 compounds as lead compounds, one of skill in the art would not have been motivated to modify the ARBs disclosed in the '902 patent to obtain olmesartan medoxomil. Specifically, the court found that the prior art as a whole taught away from the use of a hydrophilic substitute at the 4-position of the imidazole ring, relying on, *inter alia*,

the structural-activity relationship ("SAR") data in the '069 patent and the use of lipophilic groups at the 4-position in other second-generation compounds, including DuPont's '902 compounds. *Daiichi*, 670 F. Supp. 2d at 369-75. Accordingly, the district court also found that the prior art provided no motivation to modify the '902 compounds' lipophilic alkyls at the 4-position to the hydrophilic hydroxyisopropyl group of olmesartan. *Id.* at 378-80. Again we find no error in the district court's findings.

The '069 patent reveals a clear preference for lipophilic groups at the 4-position of the imidazole ring. The vast majority of the '069 compounds contain a lipophilic group at this position, as do twenty-seven of the thirty most active compounds, with two containing a neutral group and only one, Example 342, containing a hydrophilic group. J.A. 13717. This preference extends to the forty-two compounds in losartan's biphenyltetrazole series. Again, the vast majority, thirty-six out of forty-two compounds, have a lipophilic group at the 4-position and only four compounds, Examples 342, 329, 118, and 335, have a hydrophilic group. *Id.* at 7715. The few compounds with hydrophilic groups at the 4-position are drowned out by the sea of 4-lipophilic compounds, which are the essence of what the '069 patent teaches.

Three subseries analyses comparing the binding affinity of '069 patent compounds that vary only at the imidazole ring's 4-position confirm the preference for lipophilicity at the 4-position. In the series of compounds with a biphenyltetrazole substitutent at the 1-position, a propyl group at the 2-position, and a hydroxymethyl group at the 5-position (1) three out of four compounds with a lipophilic group at the 4-position exhibit higher affinity binding, measured as a lower IC_{50}, than Example 334 with a neutral group, and (2) all four compounds with a lipophilic group exhibit higher affinity binding than

Example 335 with a hydrophilic group. Specifically, Examples 124F, 124D, 124K, and 113 with lipophilic groups at the 4-position have IC_{50} values of 0.001 μM, 0.006 μM, 0.013 μM, and 0.020 μM, respectively, compared to an IC_{50} of 0.015 μM for Example 334, which has the highest binding affinity of any compound with a non-lipophilic group, and an IC_{50} of 0.26 μM for Example 335. *Id.* at 13721.

Similarly, in the series of compounds with a biphenyltetrazole substitutent at the 1-position, a propyl group at the 2-position, and a carboxylic acid at the 5-position, two out of three compounds with a lipophilic group at the 4-position exhibit higher affinity binding than Example 329 with a hydrophilic group. Specifically, Examples 265C (DuPont's DuP 532) and 251A have IC_{50} values of 0.003 μM and 0.045 μM compared to an IC_{50} of 0.076 for Example 329. *Id.* at 13720. Finally, Example 342, described above as the compound with the highest binding affinity of any compound with a hydrophilic group at the 4-position, has a lower binding affinity, higher IC_{50}, than Example 140J, which differs only by the substitution of a lipophilic group at the 4-position. *Id.* at 13725. Thus, the compounds in the prior art, including the parties' proposed lead compounds, favor lipophilic 4-substitutents rather than the 4-hydrophilic group of olmesartan medoxomil.

An analysis of regioisomer pairs in which the 4- and 5-positions are transposed provides even further confirmation. For all eight regioisomer pairs, the regioisomer with a lipophilic group at the 4-position has higher binding affinity than the regioisomer with a hydrophilic group at that position. *Id.* at 13713-16. In the 6155 series, for example, two compounds with lipophilic chlorine atoms at the 4-position exhibit ten-fold and 100-fold better binding than compounds with a hydrophilic acetic acid or hy-

droxymethyl group, respectively. *Id.* at 13713. And in the biphenyltetrazole series, losartan with a chlorine at the 4-position has two-fold higher binding affinity than its regioisomer, Example 118, with a hydrophilic hydroxymethyl group. *Id.* at 13716.

DuPont's second-generation ARBs repeat and enhance the preference for lipophilicity at the 4-position. Specifically, DuPont's DuP 532 replaces losartan's chlorine atom with a more lipophilic multiple fluorine group ($-C_2F_5$), and the six '902 compounds replace the chlorine with more lipophilic alkyl groups. No other second-generation ARB but olmesartan medoxomil has a hydrophilic group at the 4-position. *Id.* at 13722. Altogether, the '069 patent's SAR data and the structure of other second-generation ARBs counter any notion that one of skill in the art would have been motivated to modify the '902 compounds' lipophilic alkyl groups to a hydrophilic group. Such a holding would have been based on hindsight.

Mylan argues that the motivation to modify comes directly from the '069 patent and specifically from Example 118, losartan's regioisomer, with its hydrophilic hydroxymethyl group at the 4-position. According to Mylan, the parties' experts agreed that Example 118 is one of the more potent and important of the compounds disclosed in the '069 patent, and thus, Mylan argues, although Example 118 is slightly less potent than losartan, it would have motivated one of skill in the art to alter the '902 compounds' alkyl groups to a hydrophilic group. Alternatively, Mylan argues, even without the benefit of Example 118, one of skill in the art would have been motivated to make the "minor" modification of hydroxylation of the

'902 compounds' alkyls to produce a hydroxyisopropyl.[4] We disagree.

First, the SAR data in the '069 patent, described in detail above, contradict Mylan's arguments. Example 118 may be one of the more potent biphenyltetrazole compounds disclosed in the '069 patent, but it is one of only four to contain a hydrophilic group at the 4-position and one of only six to have a non-lipophilic group at that position. Furthermore its regioisomer, losartan, displays greater binding affinity as do all the disclosed regioisomers with a lipophilic group compared to a hydrophilic group at the 4-position. And while the '069 patent's SAR data do not make available a subseries analysis for Example 118, all available subseries, as described above, demonstrate a clear preference for lipophilic groups over hydrophilic ones.

Second, Mylan's argument relies on first selecting the '902 compounds, which improved on losartan by using even more lipophilic alkyl groups at the 4-position, only to reject that very feature to obtain olmesartan medoxomil. *See Eisai*, 533 F.3d at 1358 (affirming a holding of non-obviousness based in part on a finding that the record "show[ed] no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature . . . that gave [it an] advantageous property"). As the district court in this case put it, "a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics, specifically their increased lipophilicity at the 4-position." *Daiichi*, 670 F. Supp. 2d at 379.

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[4] In fact, a difference of only a single oxygen atom between Example 6 of the '902 patent and olmesartan, as noted by Mylan, is of greater significance than it superficially appears, as it is the difference between functional groups, specifically an isopropyl and a hydroxyisopropyl.

Finally, even crediting Mylan's argument that the '069 patent does not teach away from a hydrophilic group at the 4-position, the '069 patent simply does not provide a reason to make such a modification. We thus affirm the district court's decision holding that one of skill in the art would not have been motivated to modify the '902 compounds at the 4-position to obtain a compound with a hydrophilic hydroxyalkyl group.

Because we affirm the district court's findings that Mylan failed to establish either that one of skill in the art would have selected the '902 ARBs as leads or that one of skill in the art would have modified the '902 ARBs at the 4-position of the imidazole ring to obtain olmesartan medoxomil, we need not address the district court's alternative grounds for holding that Mylan failed to establish a *prima facie* case of obviousness or the court's findings on secondary considerations.

CONCLUSION

For the foregoing reasons, we affirm the district court's decision holding that claim 13 of the '599 patent was not shown to be invalid as obvious.

AFFIRMED

United States Court of Appeals for the Federal Circuit

06-1329

TAKEDA CHEMICAL INDUSTRIES, LTD.
and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Plaintiffs-Appellees,

v.

ALPHAPHARM PTY., LTD.
and GENPHARM, INC.,

Defendants-Appellants.

David G. Conlin, Edwards Angell Palmer & Dodge LLP, of Boston, Massachusetts, argued for plaintiffs-appellees. With him on the brief were Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky; and Anthony J. Viola, of New York, New York. Of counsel on the brief was Mark Chao, Takeda Pharmaceuticals North America, Inc., of Lincolnshire, Illinois.

Kevin F. Murphy, Frommer Lawrence & Haug LLP, of New York, New York, argued for defendants-appellants. With him on the brief were Edgar H. Haug and Jeffrey A. Hovden.

Appealed from: United States District Court for the Southern District of New York

Judge Denise Cote

United States Court of Appeals for the Federal Circuit

06-1329

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Plaintiffs-Appellees,

v.

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants-Appellants.

DECIDED: June 28, 2007

Before LOURIE, BRYSON, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge LOURIE. Concurring opinion filed by Circuit Judge DYK.

LOURIE, Circuit Judge.

Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. § 103. Takeda Chem. Indus., Ltd. v. Mylan Labs., 417 F. Supp. 2d 341 (S.D.N.Y. 2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin—a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes—affecting over 90% of diabetic individuals.

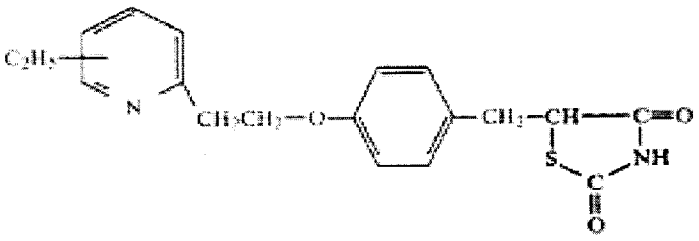
In the 1990s, a class of drugs known as thiazolidinediones ("TZDs") was introduced on the market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") first invented certain TZDs in the 1970s. Takeda's research revealed that TZDs acted as insulin sensitizers, i.e., compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPAR-gamma, which activates insulin receptors and stimulates the production of glucose transporters. Takeda, 417 F. Supp. 2d at 348-49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. Id.

Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial

success since its launch in 1999. By 2003, it held 47% of the TZD market, and gross sales for that year exceeded $1.7 billion. Id. at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

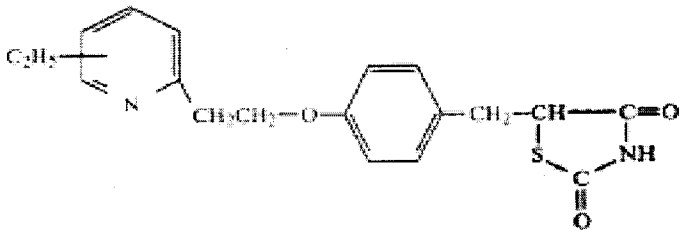
Takeda owns U.S. Patent 4,687,777 (the "'777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." '777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

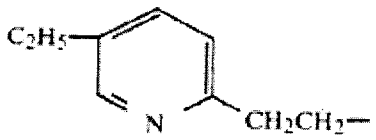
Id., claims 1 & 5.

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring.[1] That chemical structure, which has an ethyl substituent (C_2H_5) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, viz., compounds with an ethyl substituent located at the four available positions on the pyridyl ring. Takeda, 417 F. Supp. 2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

> 2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione.

'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:

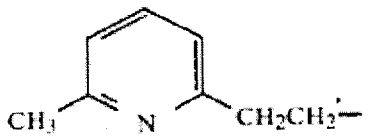


Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with

[1] Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." Takeda, 417 F. Supp. 2d at 351.

its ANDA pursuant to § 505(j)(2)(B)(ii), asserting that the '777 patent is invalid as obvious under 35 U.S.C. § 103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103. The court first concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie

case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured though inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

In this appeal, we are presented with one issue, namely, whether the asserted claims of the '777 patent would have been obvious under 35 U.S.C. § 103 at the time the invention was made. An invention is not patentable, inter alia, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1238-39 (Fed. Cir. 2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are

reviewed for clear error following a bench trial." Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1289 (Fed. Cir. 2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law, including our en banc decision in In re Dillon, 919 F.2d 688 (Fed. Cir. 1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of

Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). The Court stated that the Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. KSR, 127 S. Ct. at 1734 (quoting Graham, 383 U.S. at 17-18).

In a thorough and well-reasoned opinion, albeit rendered before KSR was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four Graham factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. Differences Between the Prior Art and the Claims

a. Selection of Compound b as Lead Compound

Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." Dillon, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. In re Grabiak, 769 F.2d 729, 731-32 (Fed. Cir. 1985).

We elaborated on this requirement in the case of In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." Id. A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." Id. We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. Id. (citing In re Jones, 958 F.2d 347 (Fed. Cir. 1992); Dillon, 919 F.2d 688; Grabiak, 769 F.2d 729; In re Lalu, 747 F.2d 703 (Fed. Cir. 1984)).

That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR.[2] While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." Id. As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id. Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

We agree with Takeda and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a

[2] We note that the Supreme Court in its KSR opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in KSR did consider the particular time at which obviousness is determined, we consider that the Court did not in KSR reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

compound with better activity.[3] Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, i.e., replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's U.S. Patent 4,287,200 (the "'200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of millions of TZD compounds."[4] Takeda, 417 F. Supp. 2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection

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[3] The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

[4] Three divisional applications derive from the '200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the "'779 Patent"). The '779 patent is of particular relevance in this appeal and is discussed below. Takeda, 417 F. Supp. 2d at 378.

in order to show that the claimed compounds of the '200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. Id. at 375.

The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." Id. at 353. The broadest claim of the '779 patent covers over one million compounds. Id. at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the

compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." Id.

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research." Id. at 380.

The court found that the three compounds that the Sodha II reference identified as "most favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. Id. at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." Id. at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that

compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda's witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that KSR, as well as another case recently decided by this court, Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir.

2007), mandates reversal. Relying on KSR, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in Pfizer, where we found obvious certain claims covering a particular acid-addition salt, directly supports its position.

We disagree. The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S. Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." Id. That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on Pfizer fares no better. In Pfizer, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically

acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. Pfizer, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of this case," we found that the prior art provided "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." Id. at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects." Thus, Pfizer does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. See Eli Lilly & Co. v. Zenith Goldline Pharms., 471 F.3d 1369 (Fed. Cir. 2006) (affirming the district court's

finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

b. Choice of the Claimed Compounds

Even if Alphapharm had established that preliminary finding, and we have concluded that it did not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. Takeda, 417 F. Supp. 2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda's experts. Id. at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. Id.

Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side

effects" and thus researchers would have been inclined "to focus research efforts elsewhere." Id. at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly from compound b in structure. Id. at 376 n.51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. Id. at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. Id. at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on In re Wilder, 563 F.2d 457 (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In Wilder, our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be

useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." Id. at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. Wilder, 563 F.2d at 460.

We would note that since our Wilder decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," Grabiak, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of Wilder. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. Takeda, 417 F. Supp. 2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone

was "comparatively potent" and "showed no statistically significant toxicity." Id. at 356-57. During the following months, Takeda performed additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. Id. at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, Wilder does not aid Alphapharm because, unlike the homolog and claimed compound in Wilder that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That

statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the '779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed supra, the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing

had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.[5]

2. Scope and Content of the Prior Art

Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 patent prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 patent and the file history that appears in the court's opinion.

We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. Takeda, 417 F. Supp. 2d at 378. In

[5] The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a prima facie case of obviousness, and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

considering the prosecution history of the '779 patent, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." Id. The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b." Id. at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, see id. at n.59, see also Custom Accessories, Inc. v. Jeffrey-Allan Indus., 807 F.2d 955 (Fed. Cir. 1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the '777 patent have not been shown to have been obvious and hence invalid.

AFFIRMED

United States Court of Appeals for the Federal Circuit

06-1329

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Plaintiffs-Appellees,

v.

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants-Appellants.

DYK, Circuit Judge, concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here—claim 2—is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 ("'777 patent")—which are also referenced in the judgment—renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art U.S. Patent No. 4,287,200 ("'200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of

unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. See Application of Petering, 301 F.2d 676, 683 (C.C.P.A. 1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); see also Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1371 (Fed. Cir. 2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 patent, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

United States Court of Appeals for the Federal Circuit

IN RE YASUHITO TANAKA

2010-1262

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in application Serial No. 10/201,948.

Decided: April 15, 2011

CHARLES GORENSTEIN, Birch, Stewart, Kolasch & Birch LLP, of Falls Church, Virginia, argued for appellant. With him on the brief were ROBERT J. WEBSTER and MICHAEL B. MARION.

BENJAMIN D.M. WOOD, Associate Solicitor, United States Patent and Trademark Office, of Alexandria, Virginia, argued for appellee. With him on the brief were RAYMOND T. CHEN, Solicitor, and NATHAN K. KELLEY, Associate Solicitor.

R. CARL MOY, William Mitchell College of Law, of St. Paul, Minnesota, for amicus curiae William Mitchell College of Law Intellectual Property Institute.

CARTER G. PHILLIPS, Sidley Austin LLP, of Washington, DC, for amicus curiae Merck & Co., Inc. With him on

the brief were JEFFREY P. KUSHAN and PETER S. CHOI. Of counsel on the brief was EDWARD W. MURRAY, Merck & Co., Inc, of Rahway, New Jersey.

HENRY C. DINGER, Goodwin Procter LLP, of Boston, Massachusetts, for amicus curiae Teva Pharmaceuticals USA, Inc. With him on the brief were FREDERICK H. REIN and ERIC H. YECIES, of New York, New York.

Before BRYSON, LINN, and DYK, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LINN.

Dissenting opinion filed by *Circuit Judge* DYK.

LINN, *Circuit Judge*.

Yasuhito Tanaka ("Tanaka") appeals from a precedential decision of the Board of Patent Appeals and Interferences ("Board") holding that a reissue application that retains all of the original patent claims and adds only narrower claims does not present the type of error correctible by reissue under 35 U.S.C. § 251. *See Ex parte Yasuhito Tanaka*, No. 2009-000234 (B.P.A.I. Dec. 9, 2009) ("*Decision*"). Because the Board's determination is contrary to longstanding precedent of this court, this court reverses and remands.

BACKGROUND

U.S. Patent No. 6,093,991 ("the '991 patent") issued on July 25, 2000, with independent claim 1 and dependent claims 2-7. It describes an "alternator pulley" that uses a one-way clutch to improve the power generation efficiency of an automobile's alternator. Exactly two years after its issue date, Tanaka filed reissue application Serial No. 10/201,948 ("the '948 application") in the

United States Patent and Trademark Office ("PTO") seeking to broaden the scope of independent claim 1 of the '991 patent. Tanaka's declaration in support of the broadening reissue stated that "the originally-presented claims did not adequately define the invention because they were more specific than necessary" and thus "the claims of the original patent cover less subject matter than we were entitled to claim." J.A. 447.

Over the course of prosecution of the reissue application, Tanaka gave up his attempt to broaden claim 1 and instead presented for reexamination unamended original claims 1-7 and new claim 16, dependent on claim 1. On September 24, 2007, Tanaka submitted a substitute reissue declaration stating that "because I did not fully appreciate the process of claiming according to U.S. practice, I did not realize that I had claimed more or less than I was entitled to claim" and "the originally presented claims did not adequately define the invention because they were more specific than necessary." J.A. 219-20.

On October 10, 2007, the examiner rejected claims 1-7 and 16 with the following explanation:

> The nature of the defect is that the error specified in the oath filed 9/24/2007 is not an error correctible by a reissue. The Applicant has not specified an error that broadens or narrows the scope of the claims of issued patent 6093991. The original claim 1 remains in the current reissue application, therefore the broadest scope of the patent remains the same.

J.A. 207. This rejection was made final and Tanaka appealed to the Board.

In a precedential opinion with a panel of seven judges, the Board affirmed the examiner's rejection. The Board found no controlling authority to guide resolution of the precise question at issue: whether the examiner "erred in determining that the presentation of a narrower claim in a reissue application that still contains all of the original patent claims does not present the type of error correctible by reissue under 35 U.S.C. § 251." *Decision* at 5. Interpreting the language of § 251 itself, the Board held that the statute "disallow[s] reissue applications that simply add narrow claims to the reissue patent when no assertion of inoperativeness or invalidity for the reasons set forth in § 251 can be made by the patentee . . . ." *Decision* at 24. The Board thus affirmed the examiner's rejection, finding that Tanaka was impermissibly seeking an additional claim on reissue "in order to hedge against the possible invalidity of one or more of the original claims." *Decision* at 19-21.

Tanaka timely appealed. This court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

In the absence of disputed facts, this court reviews the legal question of whether an applicant satisfies the statutory requirements of 35 U.S.C. § 251 de novo. *In re Serenkin*, 479 F.3d 1359, 1361 (Fed. Cir. 2007).

On appeal, Tanaka argues that the Board erred in concluding that reissue is not a remedy available under these circumstances. Tanaka argues that the Board's conclusion is contrary to the binding precedent of this court and is a direct departure from long-established practices of the PTO.

The PTO responds that the Board correctly concluded that reissue is not an available remedy in this case. The PTO asserts that omission of a dependent claim does not render a patent "partially inoperative" under § 251, because the subject matter covered by the dependent claim is necessarily covered by its antecedent independent claim. Nor does the omission of a dependent claim according to the Director, constitute "claiming more or less than the patentee had a right to claim in the patent" as required by the statute. The Director argues that because binding precedent makes clear that "claiming more or less" in § 251 refers to the scope of protection afforded by the patent, an additional dependent claim neither adds to nor detracts from the scope of protection afforded by the original patent. Because Tanaka's purported error is neither one of overclaiming nor underclaiming, the PTO contends that it is not a claiming error cognizable under § 251 and that there is no support for applying § 251 beyond its literal scope in this case.

This court concludes that the Board's determination is contrary to longstanding precedent of this court and flies counter to principles of stare decisis. Section 251, which governs the reissue of defective patents, provides in pertinent part:

> Whenever any patent is, through error without any deceptive intention, deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than he had a right to claim in the patent, the Director shall, on the surrender of such patent and the payment of the fee required by law, reissue the patent for the invention disclosed in the original patent, and in accordance with a new and amended application, for the unexpired part of the term of the original pat-

> ent. No new matter shall be introduced into the application for reissue.

35 U.S.C. § 251 (emphases added).

As interpreted by this court, the reissue statute imposes two requirements for properly invoking the reissue process. First, the original patent must be "wholly or partly inoperative or invalid." *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 882 F.2d 1556, 1564 (Fed. Cir. 1989). Second, "the defective, inoperative, or invalid patent" must have arisen "through error without deceptive intent." *Id.* at 1565. There is no dispute in this case that any defect arose without deceptive intent.

Nearly a half century ago, our predecessor court, the Court of Customs and Patent Appeals, clearly stated that adding dependent claims as a hedge against possible invalidity of original claims "is a proper reason for asking that a reissue be granted." *In re Handel*, 312 F.2d 943, 946 n.2 (CCPA 1963). The basis for the reissue application in *Handel* was nearly identical to that in this case. The patentee had mistakenly failed to include narrow claims that he had a right to claim and later sought reissue to obtain those narrower claims without proposing to cancel any broader claims encompassing the claims sought to be added. The proposed reissue claims differed from the existing claims simply by the inclusion of additional limitations.

Judge Giles S. Rich wrote the *Handel* decision reversing the Board's rejection of the reissue application. He explained that the reissue claims involved subject matter disclosed in the specification and thus were properly directed to "the invention disclosed in the original patent." *Id.* at 944. In a footnote, Judge Rich remarked that "[t]he term 'inoperative' has been construed to mean inoperative adequately to protect the invention, which may be due to

failure of the solicitor to understand the invention." *Id.* at 945 n.2 (quoting McGrady, *Patent Office Practice* 309 (4th ed. 1959)). Judge Rich added that because the original patent claims were all retained in the reissue application the "term 'less' [in Handel's reissue declaration] appears to have been used in the sense of *fewer* claims than he could properly have made, rather than in the statutory sense of subject matter included within the claims." *Id.* at 946 n.2 (emphasis in original). Thus "[t]he narrower appealed claims are simply a hedge against possible invalidity of the original claims should the prior use be proved, which is a proper reason for asking that a reissue be granted." *Id.* While this court has since characterized that view as dictum, it has not departed from it.

For example, in *In re Muller*, 417 F.2d 1387 (CCPA 1969), the Court of Customs and Patent Appeals reversed a rejection under § 251 of a reissue application that included all of the original patent claims and four additional narrower claims. The issue presented to the court was whether the new claims were improper for reissue as defining a species different from that of the original claims. The court ruled in favor of the applicant and held:

> By including an additional limitation in each of four new claims here, appellant is not shifting to different species; he is simply defining his invention more narrowly, which he could have done but failed to do in the prosecution of the patent. We find here no deliberate renunciation of subject matter, and we do not reach the question of whether a deliberate non-election of species can be remedied by reissue. We conclude that the reissue oath here shows that the failure to present the narrower claims was through error without any deceptive intention. The oath was therefore sufficient under 35 U.S.C. § 251.

Muller, 417 F.2d at 1391. Although the court did not expressly address the *Handel* case or restate the principle set forth there, the plain implication of the court's statement is that the court regarded the inclusion of dependent claims (i.e., "species") to be proper in a reissue proceeding, assuming that it was accompanied by an oath asserting that the "failure to present the narrower claims was through error without any deceptive intent." *Id.*

Years later, in *Hewlett-Packard*, this court had before it an application that, like the '948 application here, included all the original claims. 882 F.2d at 1565. Explicitly commenting on the language of footnote 2 in *Handel*, the panel in *Hewlett-Packard* observed that "the practice of allowing reissue for the purpose of including narrower claims as a hedge against the possible invalidation of a broad claim has been tacitly approved, at least in dicta, in our precedent." *Id.* The court then went on to "assume that that practice is in accordance with the remedial purpose of the statute," but upheld the invalidation of narrower reissue claims on an entirely different basis—namely, the factual inaccuracy of the affidavits submitted to the PTO in support of the reissue application. *Id.* at 1565-66.

Even though the rule that adding a dependent claim as a hedge against possible invalidity is a proper reason to seek reissue has seemingly never been formally embodied in a holding of this court or its predecessor, articulation of the rule in *Handel* was not simply a passing observation—it was a considered explanation of the scope of the reissue authority of the PTO in the context of a detailed explanation of the reissue statute. Based on this court's adoption of that rule and its adherence to the rule in both *Muller* and *Hewlett-Packard*, this court rejects the Board's contrary ruling.

This court also rejects the PTO's assertion that the omission of a narrower claim from an original patent does not constitute an error under § 251 because the omission of a dependent claim does not render the patent inoperative. While the Board correctly recognized that a patent is inoperative under § 251 if it is ineffective to protect the disclosed invention, the Board improperly assumed that Tanaka's original patent cannot be deemed partly inoperative in the absence of claim 16, whose scope is subsumed by claim 1, from which it depends. *Decision* at 17-18. This court, however, has recognized that "each claim is a separate statement of the patented invention." *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1220 (Fed. Cir. 1995). And each claim of a patent has a purpose that is separate and distinct from the remaining claims. Claims of narrower scope can be useful to clarify the meaning of broader, independent claims under the doctrine of claim differentiation. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). And dependent claims are also less vulnerable to validity attacks given their more narrow subject matter. Thus, the omission of a narrower claim from a patent can render a patent partly inoperative by failing to protect the disclosed invention to the full extent allowed by law.

Finally, this court rejects the Board's conclusion that adding a single dependent claim to the originally issued claims is equivalent to the disallowed practice of filing a "no defect" reissue. *Decision* at 20-23. This court in *In re Dien* addressed the PTO's former practice of allowing patentees to file a reissue application for the purpose of having the claims reexamined in light of newly discovered prior art without alleging a defect nor seeking any change in the patent. 680 F.2d 151, 152 (CCPA 1982). The court criticized this practice as permitting a patentee to obtain an advisory opinion from the PTO. *Id.* at 154. Here, however, there is no dispute that Tanaka has admitted error in the original prosecution, pointing out that he

neglected to seek a narrower dependent claim to which he was entitled. In addition, unlike the practice of "no defect" reissue, Tanaka's reissue application requested changes to his patent in the form of a new dependent claim. Applying for a reissue that adds only narrower claims without amending any of the original claims is not the same as a "no defect" reissue.[1]

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[1] The dissent's reliance on *Gage v. Herring*, 107 U.S. 640 (1883) for the proposition that a reissue is not proper in the absence of a surrender of subject matter is, with all due respect, misplaced. *Gage* did not address whether a reissue required that something be surrendered in the original claim(s) but instead invalidated a newly added claim that was broader than the original claim under a statute that at that time permitted correction of claims by reissue for the purpose of narrowing the claims; i.e., where the patentee claimed "more than he had a right to claim as new." *Id.* at 644-45 (citing Act of July 8, 1870, ch. 230, § 53, 16 Stat. 198). Although the Supreme Court had interpreted that statute to permit broadening reissue in certain circumstances, the Court in *Miller v. Brass Co.* cautioned that "[r]eissues for the enlargement of claims should be the exception and not the rule." 104 U.S. 350, 355 (1882). Moreover, the dissent's statement that "[h]ere, the applicants surrender nothing; they attempt to retain their rights under the original patent in their entirety" ignores applicant's compliance with § 251, which, as the dissent recognizes, requires an offer to surrender the entire original patent upon the filing of a reissue application. *See* 35 U.S.C. § 251; *Manual of Patent Examining Procedure* § 1440-58 (7th rev. 2008) ("[A]n original claim, if re-presented in a reissue application, will be fully examined in the same manner, and subject to the same rules as if being presented for the first time in an original non-reissue, nonprovisional application.").

Teva argues as amicus that the public has an interest in preventing patentees from seeking reissue only to add narrower claims because such practice limits the public's ability to rely on what is actually claimed in an issued patent. This court, however, sees no problem that is not already addressed by the equitable intervening rights statute, 35 U.S.C. § 252, "under which a court may protect investments made before reissue 'to the extent and under such terms as the court deems equitable.'" *Revolution Eyewear, Inc. v. Aspex Eyewear, Inc.*, 563 F.3d 1358, 1373 (Fed. Cir. 2009) (quoting 35 U.S.C. § 252).

This court recognizes that the reissue statute "was not enacted as a panacea for all patent prosecution problems, nor as a grant to the patentee of a second opportunity to prosecute de novo his original application." *Serenkin*, 479 F.3d at 1362 (quoting *In re Weiler*, 790 F.2d 1576, 1582 (Fed. Cir. 1986)). However, the narrow rule relating to the addition of dependent claims as a hedge against possible invalidity has been embraced as a reasonable interpretation of the reissue statute by this court and its predecessor for nearly fifty years without any obvious adverse consequences. To deviate from that long-standing interpretation would be contrary to the doctrine of stare decisis and is unwarranted.

CONCLUSION

For the foregoing reasons, this court reverses the judgment of the Board and remands for further proceedings consistent with this opinion.

REVERSED AND REMANDED

United States Court of Appeals for the Federal Circuit

IN RE YASUHITO TANAKA

2010-1262

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in application Serial No. 10/201,948.

DYK, *Circuit Judge*, dissenting.

Respectfully, I dissent. I would affirm the Board's holding that the addition of a narrower claim in a reissue application is not a proper basis for reissue under 35 U.S.C. § 251 if the application still contains all of the original patent claims.

I

The majority here bases its decision on the assertion that "the Board's determination is contrary to longstanding precedent of this court and flies counter to principles of stare decisis." Maj. op. at 5. To support this assertion the majority relies on *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 882 F.2d 1556 (Fed. Cir. 1989), *In re Muller*, 417 F.2d 1387 (CCPA 1969), and *In re Handel*, 312 F.2d 943 (CCPA 1963). In my view, none of these cases re-

solves the issue before us. Where, as here, the prior cases have "never squarely addressed the issue, and have at most assumed the applicability of [a particular] standard," we are not bound by those decisions and remain "free to address the issue on the merits" in subsequent cases. *Brecht v. Abrahamson*, 507 U.S. 619, 631 (1993); *see also Jan's Helicopter Serv., Inc. v. F.A.A.*, 525 F.3d 1299, 1308 n.9 (Fed. Cir. 2008); *Co-Steel Raritan, Inc. v. Int'l Trade Comm'n*, 357 F.3d 1294, 1307 (Fed. Cir. 2004); *United States v. County of Cook, Ill.*, 170 F.3d 1084, 1088 (Fed. Cir. 1999).

In *Handel*, the examiner rejected the reissue claims in part because the addition of narrower claims without modification of the original claims was not a proper ground for reissue. 312 F.2d at 945. The Board reversed that ground for rejection, holding instead that the reissue claims were improper because they were not "directed to the same invention recited in the claims of the patent." *Id.* at 947. On appeal, our predecessor court made clear that its "function [was] to pass only on such grounds of rejection as [had] not been reversed by the [Board]." *Id.* at 948 Thus, whether the addition of narrower claims was a proper grounds for reissue was "clearly out of the case." *Id.* at 946. The court stated explicitly that the "sole issue in the case [was] whether the [reissue] claims [were] 'for the invention disclosed in the original patent,' as required by 35 U.S.C. § 251." *Id.* at 944. Though the court stated in a footnote that reissue is proper when the only change to the original patent is the addition of narrower claims as "a hedge against possible invalidity," it did not squarely address the issue. *See id.* at 945 n.2.

In *Muller*, the reissue claims were rejected in part because "they [were] drawn to species which were not elected under a restriction requirement in the original

application." 417 F.2d at 1388. The court reversed because it concluded that the applicant was "not shifting to [a] different species." *Id.* at 1391. Far from resolving the issue before us today, the court said nothing about whether the addition of a narrower claim in a reissue application that still contains all of the original patent claims is proper.

In *Hewlett-Packard*, we made clear that we were not deciding whether to allow reissue for the purpose of including narrower claims as a hedge against invalidity. 882 F.2d at 1565. We noted that, "[f]or purposes of this case, we will assume that that practice is in accordance with the remedial purpose of the [reissue] statute," but stated explicitly that "[w]e need not decide here whether omission of narrow claims . . . meets . . . the requirement for error [under § 251]." *Id.*

None of these cases squarely addressed or decided whether seeking to include narrower claims while retaining the original claims is a proper basis for reissue under § 251. In *Hewlett-Packard* we explicitly stated that we were not deciding the issue. The earlier cases, moreover, did not address the Supreme Court decision in *Gage v. Herring*, 107 U.S. 640 (1883), discussed below. As a result, we are free to decide the issue in this case.

II

Both the language and the purpose of the statute clearly support the PTO's position. The reissue statute explicitly restricts reissue to circumstances in which the "patent is, through error . . . , deemed wholly or partly inoperative or invalid." 35 U.S.C. § 251. Thus, the statute is intended to "provid[e] the patentee with an opportunity to correct errors" within the patent. *In re Graff*,

111 F.3d 874, 877 (Fed. Cir. 1997). Here, the applicants made no correction to the original patent; instead, they merely attempted to add claims to the original patent. The required premise of the statute that the original claims were "deemed wholly or partly inoperative or invalid" as the result of an "error" is entirely missing. 35 U.S.C. § 251. There is no assertion that correction of anything in the original patent was required. The Supreme Court in *Gage* held that under such circumstances reissue is unavailable. 107 U.S. at 645.

Gage involved a patent that claimed "an improvement in [a] means for cooling and drying meal." *Id.* at 640. The original claims recited a combination of elements, including a chest, designated J, which "collect[ed] and save[d] the lighter part of the meal thrown upwards by the [drying] fan," and a rotating shaft within the chest, designated K, which "convey[ed] all the meal, after it ha[d] been cooled, dried, and collected, to the elevator." *Id.* at 643–44. The applicant contended that reissue was proper because "the original patent was too much restricted by including in the [claim] elements [J and K] which were no part of the real invention." *Id.* at 645. The applicant sought to correct this supposed error via reissue by adding a new broader claim, which deleted two of the original claim elements (J and K), while retaining the original claims. *Id.* The Court concluded that there was no mistake or error in the original patent as manifested by the retention of the original claims without modification. *Id.* The Court noted that while the applicant could have demonstrated an error by modifying the original claim, he chose not to do so. *Id.* The Court stated:

> It is plausibly suggested that 'the claim could be made perfect in form, and consistent with the description of all that portion of the apparatus

> which relates to the invention, by simply striking out the letter of designation for the upper chest, J, and the letter of designation for the conveyor shaft of that chest, K.' *But that the inventor did not and does not intend so to amend his claim is conclusively shown by his having repeated the same claim, including these very letters of designation, in the [retained] claim of the reissued patent. His attempt is, while he retains and asserts the original claim in all particulars, to add to it another claim which he did not make, or suggest the possibility of, in the original patent . . . .*
>
> *To uphold such a claim . . . would be to disregard the principles governing reissued patents,* stated upon great consideration by this court at the last term in the case of *Miller v. [Bridgeport] Brass Co.*, 104 U.S. 350, and since affirmed in many other cases.

Id. (emphases added). The cited decision in *Miller* similarly made clear that "a claim may be enlarged in a reissued patent, [but] this can only be done when an actual mistake has occurred; not from a mere error of judgment."[1] *Miller v. Bridgeport Brass Co.*, 104 U.S. 350, 355

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[1] Contrary to the majority's assertion, the Court in *Gage* did not invalidate the newly added claim because the statute in effect at that time did not permit correction of claims by reissue for the purpose of broadening the claims. The Court explicitly noted that the applicant could have corrected the alleged error in his claims by amending the original claim to broaden it in the desired manner. *Gage*, 107 U.S. at 645. Even though the statute in effect at the time of *Gage* did not explicitly permit broadening reissues, the Supreme Court, in cases arising prior to *Gage*, had interpreted the statute to permit correction of the claims by reissue for the purpose of

(1881). The applicants here attempt to do virtually the same thing as in *Gage*. By retaining the original claims without alteration or amendment, the applicants have admitted that there was no error in the original patent. The fact that no error is being corrected here, as in *Gage*, makes reissue unavailable in this case.

While our decisions, and those of our predecessor court, have held that a reissue may sometimes be proper where the original claims have not been revised, those decisions make clear that some correction of an error affecting the original claims is required. In other words, the correction of that error must have a direct and identifiable effect on the applicant's rights under the original patent. For example, where applicants were permitted to perfect priority under 35 U.S.C. §§ 119 and 120, the resulting correction to the patent had a direct impact on the applicant's rights under the original patent because all of the claims were given a new priority date. *See Brenner v. Israel*, 400 F.2d 789, 790–91 (D.C. Cir. 1968) (permitting an applicant to perfect foreign priority under 35 U.S.C. § 119 via an application for reissue); *Fontijn v.*

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broadening the claims. *See Miller*, 104 U.S. at 354–55; *Battin v. Taggert*, 58 U.S. 74, 84 (1854); *see also Topliff v. Topliff*, 145 U.S. 156, 167 (1892); 4A-15 Donald S. Chisum, Chisum on Patents § 15.02[9][a] (2011) (noting that, though the Patent Act of 1952 was the first statute to explicitly permit broadening reissue, "the Supreme Court had read [the prior statutes] as encompassing underclaiming as well as overclaiming"). As noted in the text, *Miller*, which is the lead case permitting the correction of the claims by reissue for the purpose of broadening, is in fact relied upon by the Court in *Gage*. Thus, in *Gage*, the Court found fault not with the fact that the applicant was attempting to broaden his claims, but with the fact that he did so without making any change to the original patent.

Okamoto, 518 F.2d 610, 621–23 (CCPA 1975) (permitting an applicant to perfect a priority claim under 35 U.S.C. § 120). And in a case where the applicant was permitted to correct the lack of antecedent basis in a claim, the correction directly affected the applicant's rights under the patent because it preserved the validity of the claim. *See In re Atenpohl*, 500 F.2d 1151, 1156–57 (CCPA 1974). In each of those cases a correction was made to the original patent.

Here, the addition of the dependent claims has no impact on the applicants' rights under the original patent. The original claims were not changed, and the addition of new claims has no effect on the applicants' rights under the original claims. The applicants effectively attempt to retain their rights under original patent while securing a second patent which covers the subject matter of the dependent claims.

This is, moreover, directly contrary to another aspect of the reissue statue, which requires "surrender of [the original] patent." 35 U.S.C. § 251. As a condition of reissue, § 251 requires that the applicant relinquish any claim to the original patent—"the patentee has no rights except such as grow out of the reissued patent." *Eby v. King*, 158 U.S. 366, 373 (1895). Here, the applicants surrender nothing; they attempt to retain their rights under the original patent in their entirety.